Drug Substance Risk Assessment
Report from Breakout Session

Moderators: Ira Berry, Eric Duffy, Marie Kowblansky, Chris Oldenhof, Edwin Ramos, Bill Regan, Paul Schwartz, John Smith, Jean Wyvratt

AAPS Workshop, June 12, 2001

Basis for Low Risk Drug Substance

- Most Critical
  - Specifications/Quality Assessment
  - Manufacturer
- Consider
  - Stability

    understood & well-controlled degradation

    vs. no degradation

Basis for Low Risk API (contd.)

- Less Critical
  - Structure
    - simple vs. complex not relevant
    - analytical methodology available to assess all classes
  - Manufacturing Process,
    - must be well understood (how is this defined?)
  - Reactivity
    - stress stability to understand, in drug product

Quality Controls

- Specifications
  - Justified specifications
  - Availability of sound analytical methods
  - Upgrade to Contemporary Guidances?
    - many felt updating necessary to consider API (ICH)
    - concern about updating analytical methods
      - new impurities detected, mass balance
      - need to define mechanism for in-use qualification of impurities

Quality Controls (contd.)

- Specifications vs. Change Assessment Protocol
  - should specifications alone provide ability to assess the impact of change
  - importance of comprehensive impurity profile method for change evaluation

Process Characteristics

- Most important is **well-controlled** process
- In-process controls
  - defined for individual process
- Simple vs. complex
  - not considered relevant
  - can this be defined by number of steps/yield?

Process Characteristics (contd.)

- Process Robustness
  - not definable without a manufacturing history
  - consistency of manufacturing in absence of change does not necessarily define this
  - process capability indices as a measure

Acceptable Historical Data

- Individual firms would need to be qualified based on their manufacturing & GMP history with specific drug

  (*firm = NDA/ANDA or DMF holder?)*
- Failure rate/annual reviews/deviations
- Number of successful batches/years/campaigns
  - warranty concept
- Key expectation: GMP compliance exists

Drug Substance/Dosage Form Link

- Connection exists for certain attributes
  - physical property issues for certain dosage forms
  - impurity issues for all dosage forms
  - could decouple drug substance and product, if appropriate specifications are in place

Concerns

- If a drug substance is listed as low risk, does every manufacturer have to participate
  - no obligation

- Does this approach lead to universal specifications for a given drug substance

Action Items

- Clearly define "risk" that is being addressed
- Can API be qualified as low risk separate from dosage form?

  What types of lists (drug substance, drug product, manufacturer, manufacturing site) would be developed for low risk drugs?
- Define a list of low risk compounds, then assess why they qualify
  - acetaminophen, ibuprofen, captopril….

Principle: Drug substances may need to be considered in the context of the drug product. Company-to-company variability? Drug substance from one company may be well characterized, but may not be from another company.

Specifications

- Most compounds under this concept will have USP monographs. However, USP monographs are inadequate in many cases. Monographs do not address process-specific impurities. Monographs may use antiquated methodology (TLC).
- Need to meet ICH quality standards (impurities and residual solvents) at a minimum.
- Assay for drug substance 99.0 –101.0% - ideal specification, but some have 90-110%. Can we establish an ideal specification? What would it be? NLT 96%? Is the boundary determined by the drug substance itself and the data presented? Perhaps 98 is ok in one case, 95 in another. Analytical variability enters into this discussion. 98-102 the most common specification for new USP monographs. If drug substance meets 98-102 at end of shelf-life, then is it stable?
- Specification should consider specificity and variability of method.
- If company has already received approval for a specification, then why tighten? Specification. vs. process variability in assessing change.
- Should we consider mass balance rather than assay?
- Key is that the drug substance is well characterized and well-known.
- Specifications as an aggregate should insure low-risk – perhaps not on a test-by-test basis.
- Close limits set on amounts of unknown and unqualified impurities. Focus on qualification (is this part of ICH)?
- Need to use ICH Q6A to set specifications (consider process variability as well as safety)
- "Meet specification" isn't always sufficient to justify manufacturing change.
- Increase level of solvent within ICH Q3C specifications. – safety based on exposure to solvent vs. safety based on performance in drug product manufacture.
- If change specifications – prior approval as per FDAMA
- This initiative does not reduce manufacturer's responsibility to collect data to justify the change.
- FDA will approve set of specifications as part of the application as a low-risk drug substance.
- GMP group will cover manufacturing change process and control.
- Specifications are sufficient to characterize drug substance.
- Need to understand the mass balance – role in determining well-characterized aspect of molecule.
- Impurities may have different response factors than drug substance. – need to include in assessment of mass balance (true vs. apparent mass balance)

Process

- Key is that process is well controlled. It is not as critical that process is simple or complex.
- BACPAC 1 definition of equivalence – apply to concept of whether manufacturer produces same material every time.
- Single route of synthesis only will yield molecule. Bond-breaking/making. Is this practical? GMP change control reduces this concern with multiple routes?
- Specifications will limit unknown impurities – IF analytical methodology is capable of detecting impurities. In this case, the risk of multiple routes is reduced.
- If process controls polymorphic form, then the polymorphic form drug substance can be low risk.
- Need to have specification for drug substance polymorphic form. Also linked to drug product
- If process and specifications control stereochemistry, then drug substance with chiral centers can be considered low-risk.

Stability

- Compounds known to be reactive (e.g. vitamin A derivatives) represent a greater risk.
- Stability under stress conditions can be used to assess reactivity.
- Impact of container/closure?
- Can we define list of "reactive" compounds?
- Reactivity spans a spectrum (low, moderate, high).
- Drug substance reactivity should be assessed in drug product context; reactive drug substances can be successfully formulated.
- BCS-like concept (classification) for topic of reactivity?
- Detailed kinetic studies of every reaction pathway may not be feasible.
- Intrinsic reactivity may impact drug product manufacture (e.g. low-light conditions, N2 blankets)
- Is reactivity only a consideration in drug product manufacture?
- Is reactivity only a consideration in drug product formulation and stability?
- If solvents/moisture not properly controlled, then may see degradation? If solvents/moisture are controlled (required for well-characterized compound), then is it still low-risk? May see reactivity with drum liner. Is change in drum liner covered under GMPs?
- Does intrinsic reactivity automatically remove drug substance from low-risk list? – no, but does require further discussion.
- For older drugs, this data may not be present. Company would have to develop this data.
- If drug substance is adequately characterized with a known stability profile and storage condition, then drug substance can be characterized as low-risk.

In-process controls

- Is not predictive. Is process specific.
- May change with process change.
- Are IPC what you would use to characterize equivalence via BACPAC 1?
- Change control (GMP) will ensure that manufacturing changes are properly considered and data gathered.

Specifications

- Particle size an exception? no Particle size is a specification if critical to drug product.

Historical data

- Historical data – should be specific to manufacturer
- Consensus is #batches under GMP conditions
- Ratio of batches made vs. batches failed
- Generics approved on the basis of one batch (the biobatch) but is supported by data from innovator
- Do not know how many batches made under an individual DMF.

Use of a product monograph?

Introduced key concept from previous session: Manufacturer's experience with API is key
Comments on this concept: none in this session

Definition of Risk

- One element of risk is a false positive (didn't release batch that was ok) vs. false negative (release batch that shouldn't).
- Risk to change in quality is the focus – not risk to safety or efficacy.
- Only change is in FDA review – not in the data collected or actions taken by the company. Must have high degree of confidence in control of process and in specifications.
- Risk associated with change – will quality changes be detected?
- Strong, state-of the art analytical methods help reduce risk and increase confidence.
- Firm can do additional testing beyond specifications to confirm that there has been no adverse impact on quality. However, how does FDA assess this additional testing? Should these additional tests be part of the specifications?
- Use of comparability protocol to define additional testing and acceptance critieria to reduce risk.
- Change vs. deviation (unplanned). Planned change should not represent increased risk; increased risk comes from unplanned deviations. Annual quality review will assess the state of control (robustness control) of the process. Annual quality review is GMP requirement and reduces risk as well.
- If process change requires a change in specification, then it is prior approval as per FDAMA.
- Must be strong, capable change control system for this proposal to be effective.
- Guidance cannot cover instances where suppliers do not inform downstream customers. Customer should consider whether to audit supplier, cover responsibilities in contract with supplier. Is this a GMP issue?
- Low-risk is NOT risk free.
- Key concept is that the manufacturer must follow of cGMPs and regulatory expectations.
- Wide industry experience with a single molecule (22 generic approvals for single API, which would appear to be unstable)

Is there a need to consider drug product in assessing API risk?

- Is relevant, but not universally. API manufacturer needs to consider possible impact of change on drug product customer. API manufacturer needs to communicate with drug product customer. Is this also a GMP issue?
- Solid dosage form (may require drug product link) vs. prior to final solution step (may not require drug product link)
- BACPAC 1 vs. BACPAC 2 changes – BACPAC 2 may require drug product supporting data
- What about API's used in multiple drug product forms? Isn't it better to consider API in isolation?

Are specifications sufficient to assess API quality?

- Need to justify the tests being performed (delete useless tests). CTD includes section titled justification of specifications. This rationale is key in establishing specifications.
- For old API, is an upgrade to ICH specifications value added? – multiple individuals expressed this concern. What about items such as NaCl and glucose as drug substances? Justification for not upgrading these type of API could be provided. The company should be able to provide justification for not following guidance based on good science.
- For an old API, is there a risk in developing these data packages? Newly identified discovered impurities would be qualified if they had always been present in the API at that level. A company would need to invest resources in developing new analytical procedures and in developing an impurity profile based on a number of historical lots.
- Second comment verifying usefulness of comparability protocol.
- Do manufacturers run routinely an abbreviated set of tests to do batch release? Then if manufacturers make changes, then are the specifications sufficient to justify the change? Additional tests could be incorporated into comparability protocol to justify process change. Specific protocol vs general change protocol? Should be driven by good science and data.

Drug substance characteristics

- Understanding of compound/process by the company and the control the company has over the process is the key – not complexity or reactivity of the compound. If process is known and controlled, then the risk is low. – multiple participants made this point.
- Not all companies have excellent controls. Should low-risk compounds be defined on the intrinsic properties of the compounds itself?
- The group did not feel that a practical working definition of "complex molecule" could be developed.
- Is reactivity of API a concern for formulation (e.g. reacts with water)? Or for API production?
- The more complex the API, the more important it is to have strong analytical methods and specifications. (e.g. tests for polymorphs, chiral purity).

Process for declaring API low-risk

- Should a basic list of low-risk API be developed? Should companies petition to have their [complex] API declared low risk? – could include compounds under patent protection.
- Is there a common set of criteria that could be developed for this petition?
- Is the basic list the first tier (slice of pie), and complex molecules added in subsequent tiers (larger slices of pie)?
- If company petitions the Agency to have their API declared low-risk, and the Agency accepts this recommendation, would this information be made public? – out of scope.

Historical experience

- 10-30 batches
- 25 batches
- >30 batches?
- Degree of knowledge increases with time, therefore, the degree of risk decreases.
- Batches vs. years? Group overwhelmingly voted for #batches.
- Combination of batches and years?
- Analogy with Canada's old drug system (7 years for each manufacturer)?

Stability

Is there a uniform set of specifications across manufacturers? What if manufacturer A meets 94% and manufacturer B meets 98?

Define "sufficient knowledge of the molecule"
You know what you know, but don't know what you don't know.

Process characteristics

Process Capability Indices used assess capability of the process – discussed in the GMP breakout group.
Use of yield and number of steps to define complexity of process?

Key point: Work to justify a manufacturing change is the same, only the filing requirements change.

Relationship between low risk initiative and BACPAC process. Is assessment of change impact more effectively addressed by BACPAC?

Specifications (includes tests and methods) – may depend on dp

- Specifications that are adequate to control a known process may not be adequate to assess process changes. Should process change be considered a GMP issue?
- Is it necessary to update older APIs which have been controlled satisfactorily for a number of years to ICH? These specifications are approved and have been judged acceptable to control the quality of the API. There should be mechanism for justifying the appropriateness of specifications.
- Is USP adequate? Consensus is no. Impurity requirements are seen as less rigorous than ICH. However, USP does have a mechanism to address labelled and unlabelled impurities.
- ICH should be starting point for determining specifications. ICH discusses impurities.
- Value added in updating specifications to ICH was questioned.
- Does there need to be a uniform set of specifications for all manufacturers making a given API? Could the Agency set these? Then anyone wishing to produce this compound would meet these criteria, and be able to market a low risk compound. Given the link between process and specifications, is this attainable?
- Changing specifications is outside the scope of this proposal. Will require a prior approval supplement.
- Need for adequate impurity profile needed to assess risk of compound.
- May need to add specifications to address polymorphism and/or particle size. If prior to the final solution step, then particle size is moot.

Stability

- Key point is to have a known, consistent stability profile. Are degradation products known? What is the toxicity of the degradants?
- Rate of degradation does not determine the risk of the compound.
- Need to know sensitivity of molecule to moisture or other environmental factors. These factors are intrinsic to the molecule and will not change with manufacturing process. These factors need not eliminate a drug from a low-risk category. However, these compounds may need to be examined more carefully.

Simple vs. Complex Molecule

- Complexity of the molecular structure does not necessarily determine its risk.
- With the analytical techniques available today, chirality can be controlled.
- Can secondary and tertiary structure of proteins be measured?
- Need to evaluate on a case-by-case basis.

Manufacturing process

- This proposal does not relieve manufacturer of the responsibility to monitor the process; testing must be linked to process.
- Manufacturing process does not necessarily exclude a molecule from the low-risk category. The key is that the impurity profile is known and impurities are qualified. May need to examine natural products, fermentation products, and semi-synthetic compounds more carefully. For example, there is a long history of manufacturing history with penicillin and other antibiotics.
- Length of synthesis is not necessarily define the complexity of the molecule. The key is to have a well-controlled process.

Low risk compounds

- What compounds are manufactured by multiple manufacturers by multiple acceptable processes? Examples given by the audience are:
  - Acetomenophen
  - Ibuprofen (may not meet ICH standards?) – grandfather?
  - Captopril
- Perhaps these compounds should be examined for the attributes that distinguish them as low risk.

GMP status of the manufacturer

- Considered to be a key component of low-risk.

Manufacturing History

- x number of batches or y years whichever comes first
- Number of campaigns should be considered
- Should be firm specific
- Validation batches do not count towards total.
- Batches need to be manufactured under cGMP conditions.

Reactivity

- Captured in the justification for specifications. See also stability.

In-process controls

- Should be included in justification of compound/process as low risk